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### INTRATHECAL BACLOFEN

*Gablofen Intrathecal*

*Lioresal Intrathecal*

#### **Drug Regimen Review Center**

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## Contents

Background .....	3
Use in spasticity and disease overview.....	3
Methodology.....	5
Intrathecal and oral baclofen products and indications .....	6
Table 1. Intrathecal and oral baclofen products and indications (from Lexicomp and Micromedex) .....	6
Off-label use evidence (Micromedex).....	8
Safety .....	8
Black Box warning.....	9
Clinical Guidelines .....	9
Table 2. Clinical guidance for the use of intrathecal baclofen .....	11
Systematic review evidence.....	13
Factors to consider.....	14
Utah Medicaid Utilization Data.....	16
Summary.....	16
A. Table 3. All patients .....	18
B. Table 4. Pediatric patients .....	19
C. Table 5. Pharmacy claims .....	20
D. Age and gender – All patients .....	21
E. Patients with diagnosis codes submitted for severe spasticity .....	22
F. Compounded intrathecal baclofen .....	22
Conclusions .....	23
Appendix 1 – Systematic Reviews.....	24
Table 1. Cochrane Systematic Review(s) – focusing on intrathecal baclofen .....	24
Table 2. Other Reviews included in the Cochrane Library: Centre for Reviews and Dissemination (CRD): Systematic reviews that meet the criteria for inclusion on <i>Database of Abstracts of         Reviews of Effects</i> (DARE) – focusing on intrathecal baclofen.....	25
Table 3. Cochrane Systematic Review(s) – Interventions for spasticity .....	25
References .....	28

## Background

Baclofen is a gamma-aminobutyric acid (GABA) agonist and its precise mechanism of action has not been fully determined.<sup>2,3</sup> It is a central nervous system (CNS) muscle relaxant that acts at the spinal cord level inhibiting the transmission of both monosynaptic and polysynaptic reflexes.<sup>3</sup> It has general central nervous system depressant effects, and may have antinociceptive effects based on animal studies.<sup>3</sup> Only a small amount of the oral dose crosses the blood-brain barrier, and the oral dose is limited by excessive sedation.<sup>2</sup> Intrathecal baclofen is administered directly into the intrathecal space (spinal fluid surrounding the spinal cord and brain) via a catheter that is attached to a refillable implanted pump.<sup>2,4</sup> The pump is refilled every few months based on dosing calculations with the programming device.<sup>5</sup> Much lower doses are required to reduce spasticity when intrathecal baclofen is administered because higher local concentrations are achieved, helping to minimize excessive sedation.<sup>4</sup>

## Use in spasticity and disease overview

Intrathecal baclofen is used in the management of severe spasticity of cerebral or spinal origin in conditions such as cerebral palsy, multiple sclerosis, or certain injuries to the spine.<sup>5,6</sup> This allows other treatments such as physical therapy to be more effective.<sup>7</sup> Spasticity can be painful causing sleep disturbance. It may interfere with mobility, exercise, and joint range of motion; it can cause speech (spastic dysarthria) or swallowing difficulties (spastic dysphagia), and affect the overall quality of life of patients.<sup>8</sup> Spasticity may have advantages for some patients which may include maintaining postural control, maintaining muscle bulk, and supporting circulatory function (may prevent formation of deep vein thrombosis).<sup>8</sup> It is important to consider whether patients would benefit from spasticity reduction, because not all would.

Intrathecal baclofen is indicated for use in patients that are unresponsive to oral antispasmodics and/or if patients experience unacceptable side effects. Patients with spasticity of cerebral origin must be one year post brain injury to be considered for intrathecal baclofen therapy (ITB).<sup>1,6</sup>

### Spasticity in children (including cerebral palsy)

The most common cause of spasticity in children is cerebral palsy (CP), but could also be caused by congenital conditions, traumatic brain or spinal cord injuries, central nervous system tumors, metabolic disorders, and hydrocephalus.<sup>4,9</sup> Based on population studies, the Centers for Disease Control and Prevention (CDC) reports prevalence estimates of CP ranging from 1.5 to more than 4 per 1,000 live births or children of a defined age range.<sup>10</sup> The CDC tracks CP through the Autism and Developmental Disabilities Monitoring (ADDM) CP Network. According to a 2008 ADDM CP Network report on 8-year-old children living in areas of Alabama, Georgia, Missouri, and Wisconsin, CP was more common among boys than among girls, and more common in black children than white children (Hispanic and white were equally likely). Most (77.4%) of these children with CP had spastic CP.<sup>10</sup> Spasticity affects daily activities and can be painful. Treatment of spasticity requires a careful pretreatment assessment using valid and reliable clinical instruments so that the most appropriate treatment options are selected. Also, "...importantly, specific, measurable, achievable, and realistic treatment goals should be delineated."<sup>4</sup> Treatment options mentioned in the literature include pharmacological (e.g., baclofen, clonidine, tizanidine, botulinum toxin, intrathecal baclofen) and non-pharmacological interventions (e.g., casting splints and stretches).<sup>4,11</sup> In patients with brain injuries, behavioral and cognitive issues associated with the injuries may complicate matters.<sup>11</sup>

## Multiple sclerosis

Demyelinating diseases are neurological disorders defined by the destruction of central nervous system (CNS) tissue and are typically immune-mediated conditions.<sup>12,13</sup> Multiple sclerosis (MS) is the most common demyelinating disorder and is characterized by inflammation, demyelination, scarring, and neuronal loss.<sup>12,13</sup> Patients with MS can exhibit benign illness to a debilitating disease resulting in significant lifestyle changes.<sup>12,13</sup> Multiple sclerosis affects nearly 400,000 individuals in the United States and 2.5 million individuals worldwide.<sup>14-16</sup> Prevalence is higher in women than men and the disease is usually diagnosed between the ages of 20 and 50 years.<sup>14,15,17</sup>

The cause of multiple sclerosis is not known.<sup>12,13</sup> Both genetic (race and gender) and environmental factors (geographical location, exposure to the sun, birth month) are linked to the disease.<sup>18-20</sup> Immunology also plays a role; MS is thought to be an auto-immune disease mediated by T-cells that compromise the blood brain barrier and allow inflammatory mediators to enter and attack the CNS. Diagnosis of MS is based on clinical symptoms in combination with evidence of lesions on magnetic resonance imaging (MRI). Symptoms vary depending on the location and severity of the CNS lesions and may include sensory loss, optic neuritis, weakness, paresthesias, ataxia, tremor, fatigue, cognitive changes, and bladder dysfunction.<sup>12,13</sup>

Multiple sclerosis (MS) is a chronic disease that can progress intermittently or continuously and is divided into four disease courses: relapsing-remitting multiple sclerosis (RRMS), primary-progressive multiple sclerosis (PPMS), secondary-progressive multiple sclerosis (SPMS), and progressive-relapsing multiple sclerosis (PRMS).<sup>12,13</sup> Relapsing-remitting multiple sclerosis is the most common form of MS and is characterized by exacerbations of neurological dysfunction followed by remissions.<sup>21</sup> RRMS may eventually develop into secondary progressive multiple sclerosis which is characterized by a neurologic deterioration with or without relapses. Primary progressive multiple sclerosis occurs in 10-15% of patients with MS and is characterized by disease progression with some minor improvements and without any exacerbations.<sup>20,22</sup> Progressive relapsing multiple sclerosis affects less than 5% of patients and is characterized by disease progression with acute relapses. Most medications used in the treatment of MS are indicated in the treatment of RRMS or SPMS; there are currently no medications labeled for use in PPMS.<sup>12,13</sup>

Treatment of MS varies depending on the clinical subset of MS present and individual patient characteristics.<sup>12,13,15,17</sup> In general, treatment may include disease modifying agents in combination with symptomatic treatment.<sup>12,13</sup> Symptomatic treatments include glucocorticoid therapy, benzodiazepines, muscle relaxants, anticonvulsants, antidepressants, and medications used to treat urinary disorders.<sup>12,13</sup> Currently, no curative medication therapies are available in the treatment of MS.<sup>15,17</sup> Disease-modifying agents provide symptomatic relief and reduced disease progression.

## Stroke

In clinical practice, treatment options for spasticity management in stroke include rehabilitation therapy, oral medication, injection therapy, orthopedic surgery, neurosurgery, and intrathecal baclofen.<sup>8</sup> Intrathecal baclofen may benefit some patients with residual spasticity.<sup>8</sup> Nonetheless, Jennifer Doble, PT, MD, states that “it does not help apraxia, does not cure aphasia, it does not make the impaired side ‘normal’, does not take away the CVA, does not cure neurogenic bladder/bowel issues.”<sup>8</sup>

## **Methodology**

Micromedex, Lexicomp, and the product labels were first searched for FDA-approved indications, off-label use and product information.

Cochrane Library literature searches for systematic reviews were conducted. Medline (PubMed), Up to Date, the Agency for Healthcare Research and Quality (AHRQ), the U.S. Department of Health and Human Services website, the FDA website, The American Academy of Neurology (AAN) website, Micromedex, and Lexicomp were searched for safety information, systematic reviews, clinical trials, and other guidelines. References of relevant search results were screened.

Reimbursement documents, health plan documents including prior authorization documents, and any relevant diagnosis coding documents were reviewed for information on billing to inform data extraction (claims data).

## Intrathecal and oral baclofen products and indications

Table 1. Intrathecal and oral baclofen products and indications (from Lexicomp and Micromedex)<sup>3,23</sup>

	Product	Indication(s)	Appropriate use	Dosing
Intrathecal	<b>Solution (Gablofen Intrathecal)</b>	Management of severe spasticity of spinal cord origin (eg, spinal cord injury, multiple sclerosis) or cerebral origin (eg, cerebral palsy, traumatic brain injury) in patients ≥4 years; may be considered as an alternative to destructive neurosurgical procedures.	<ul style="list-style-type: none"> <li>Only use in an FDA-approved implantable pump for intrathecal baclofen administration</li> <li>Health care providers should be experienced with chronic intrathecal infusion therapy</li> <li>Resuscitative equipment should be readily available</li> <li>Patient should be infection-free</li> <li>Test dose before implanting pump</li> <li>Monitoring: Monitor closely during the initial phase of pump use and when adjusting/changing dosing rate and/or concentration</li> <li>Education: Patients and caregivers on proper home care of the pump and insertion site.</li> <li>Refilling implantable pump: Use extreme caution; "pumps should only be refilled through the reservoir refill septum. Inadvertent injection into the subcutaneous tissue can occur if the reservoir refill septum is not properly accessed. Some pumps are equipped with a catheter access port that allows direct access to the intrathecal catheter; direct injection into this catheter access port or inadvertent injection into the subcutaneous tissue may cause a life-threatening overdose."</li> <li>Discontinuation: Reduce baclofen slowly (except in overdose related emergencies)</li> </ul>	<b>ADULTS</b> <ul style="list-style-type: none"> <li>"intrathecal test dose, 50 mcg in 1 mL INTRATHECALLY given over at least 1 minute; may increase dosage by 25 mcg increments every 24 hours until a 4- to 8-hour positive clinical response is demonstrated. Patients must respond to a single bolus dose of no greater than 100 mcg/2mL to be acceptable candidates for chronic therapy with the intrathecal infusion pump</li> <li>post-implant titration, initial (test dose efficacy less than 8 hours), the initial daily dose is double the screening dose administered INTRATHECALLY over 24 hour</li> <li>post-implant titration, initial (test dose efficacy greater than 8 hour), the initial daily dose is the same as the screening dose administered INTRATHECALLY over 24 hours</li> <li>post-implant titration, spinal cord spasticity, no dosage increases during first 24 hours; may slowly increase INTRATHECAL dosage by 10% to 30% once every 24 hours</li> <li>post-implant titration, cerebral origin spasticity, no dosage increases during the first 24 hours; may slowly increase INTRATHECAL dosage by 5% to 15% once every 24 hours</li> <li>post-implant maintenance, spinal cord spasticity, INTRATHECAL daily dose may be increased by 10% to 40% (MAX 40%) OR reduced by 10% to 20% as needed during periodic pump refills. Most patients require gradual increase in dose over time to maintain optimal response. Maintenance dosages usually range between 300 to 800 mcg/day (range 12 to 2003 mcg/day)</li> <li>post-implant maintenance, cerebral origin spasticity, INTRATHECAL daily dose may be increased by 5% to 20% (MAX 20%) OR reduced by 10% to 20% as needed during periodic pump refills. Most patients require gradual increase in dose over time to maintain optimal response. Maintenance dosages usually range between 90 to 703 mcg/day (range 22 to 1400 mcg/day)"</li> </ul>
	10000 mcg/20 mL (20 mL)			
	20000 mcg/20 mL (20 mL)			
	40000 mcg/20 mL (20 mL)			
	<b>Solution (Lioresal Intrathecal)</b>			
	0.05 mg/mL (1 mL)			
	10 mg/20 mL (20 mL)			
	10 mg/5 mL (5 mL)			
	<b>Solution (Lioresal Intrathecal Intrathecal)</b>			
	40 mg/20 mL (20 mL):			
	<b>Solution Prefilled Syringe (Gablofen Intrathecal)</b>			
	50 mcg/mL (1 mL)			
	10000 mcg/20 mL (20 mL)			
	20000 mcg/20 mL (20 mL)			
	40000 mcg/20 mL (20 mL)			

	Product	Indication(s)	Appropriate use	Dosing
				<b>PEDIATRICS</b> <ul style="list-style-type: none"> <li>• “(2 to 7 years old) 10 to 15 mg/day ORALLY (2 to 3 divided doses); may increase by 5 to 15 mg/day increments every 3 days to a MAX dose of 40 mg/day (3 to 4 divided doses)</li> <li>• (8 years and older), 10 to 15 mg/day ORALLY (2 to 3 divided doses); may increase by 5 to 15 mg/day increments every 3 days to a MAX dose of 60 mg/day (3 to 4 divided doses)</li> <li>• intrathecal test dose, 25 to 50 mcg INTRATHECALLY given over at least 1 minute; may increase dosage by 25 mcg increments every 24 hour until a 4- to 8-hour positive clinical response is demonstrated. Patients must respond to a single bolus dose of no greater than 100 mcg/2mL to be acceptable candidates for chronic therapy with the intrathecal infusion pump</li> <li>• post-implant titration, after the first 24 hour, the INTRATHECAL daily dose should be increased slowly by 5% to 15% only once every 24 hour, until the desired clinical effect is achieved</li> <li>• post-implant maintenance, INTRATHECAL daily dose may be increased by 5% to 20% (MAX 20%) OR reduced by 10% to 20% as needed during periodic pump refills. Most patients require gradual increase in dose over time to maintain optimal response. The average maintenance dose for children under age 12 years is 274 mcg/day (range 24 to 1199 mcg/day)”</li> </ul>
Oral	<b>Suspension (First-Baclofen 1 Oral)</b>  1 mg/mL (120 mL)  <b>Suspension (First-Baclofen 5 Oral)</b>  5 mg/mL (60 mL)  <b>Tablets (Baclofen Oral)</b>  10 mg (100)  20 mg (100)	Management of reversible spasticity associated with multiple sclerosis or spinal cord lesions	“Efficacy of oral baclofen has not been established in patients with stroke, Parkinson disease, or cerebral palsy; therefore, use is not recommended. Not indicated for spasticity associated with rheumatic disorders. Use with caution when spasticity is utilized to sustain upright posture and balance in locomotion, or when spasticity is necessary to obtain increased function.”	5 mg ORALLY 3 times a day; may increase dosage by 15 mg/day increments every 3 days to a MAX dose of 80 mg/day (3 to 4 divided doses)

## Off-label use evidence (Micromedex)

Uses other than for the treatment of spasticity are off-label (investigational). Off-label uses listed in Micromedex for intrathecal baclofen include treatment of dystonia and stiff-man syndrome.<sup>3</sup> There appears to be some evidence that indicate evidence favors efficacy in the treatment of dystonia, and it is suggested that it may be effective in treating uncomplicated dystonia.<sup>3,24-26</sup> Based on some limited evidence, it has effectively treated stiff-man syndrome in isolated cases.<sup>3,27</sup>

## Safety

Please refer to the product labeling for complete information.

Adverse events associated with intrathecal baclofen are related to CNS side-effects to baclofen itself and adverse events related to the catheter-pump device and implant procedures.<sup>4,28</sup> These include catheter dislodgement from the intrathecal space, catheter breakage or malfunction, implant site infections, or fluid collections around the pump.<sup>4,28</sup> Intrathecal mass formation at the implanted tip has been reported mostly involving pharmacy compounded analgesic admixtures, and neurosurgical evaluation to determine whether neurological symptoms are spasticity/disease related or suggestive of a intrathecal mass is recommended and/or an appropriate imaging study in some cases.<sup>1,23</sup> Elderly patients are at increased risk to experience adverse CNS effects especially at higher doses.<sup>23</sup>

Intrathecal baclofen (Lioresal and Gablofen) should be administered intrathecally and is contraindicated for intravenous, intramuscular, subcutaneous or epidural administration.<sup>1,6</sup>

Patients should be carefully evaluated and screened to determine whether intrathecal baclofen is an appropriate treatment option given the risks of complications associated with its delivery (surgical implantation and dosing). It is important to monitor patients carefully and to be cautious when determining intrathecal baclofen doses. Initial test doses and adjustments are needed during the first months, and transcutaneous refills are required throughout treatment at appropriate intervals. Caution is also advised during reintroduction of therapy after a period of interruption.<sup>23</sup> Overdose symptoms may appear suddenly or insidiously; signs or symptoms may include "drowsiness, dizziness, somnolence, hypothermia, respiratory depression, seizures, rostral progression of hypotonia and loss of consciousness progressing to coma."<sup>23</sup>

There is not only a risk for overdose, but also for underdosing which could result in withdrawal that is serious and potentially fatal.<sup>4</sup> If doses are not maintained at appropriate intervals which could be due to a missed or late refill or malfunctions in the catheter or pump, withdrawal could occur. Withdrawal symptoms include itching, exacerbated spasticity, blood pressure changes, altered mental status, fever, rhabdomyolysis, and seizures.<sup>4</sup>

Most common adverse reactions of intrathecal baclofen in patients with spasticity of spinal origin included somnolence, dizziness, nausea, hypotension, headache, convulsions and hypotonia.<sup>1,6</sup> Most common adverse reactions of intrathecal baclofen in patients with spasticity of cerebral origin included agitation, constipation, somnolence, leukocytosis, chills, urinary retention, and hypotonia.<sup>1,6</sup>



## Black Box warning

**“WARNING: DO NOT DISCONTINUE ABRUPTLY**

*See full prescribing information for complete boxed warning*

Abrupt discontinuation of intrathecal baclofen, regardless of the cause, has resulted in sequelae that include high fever, altered mental status, exaggerated rebound spasticity, and muscle rigidity, that in rare cases has advanced to rhabdomyolysis, multiple organ-system failure and death.

Prevention of abrupt discontinuation of intrathecal baclofen requires careful attention to programming and monitoring of the infusion system, refill scheduling and procedures, and pump alarms. Patients and caregivers should be advised of the importance of keeping scheduled refill visits and should be educated on the early symptoms of baclofen withdrawal. Special attention should be given to patients at apparent risk (e.g., spinal cord injuries at T-6 or above, communication difficulties, history of withdrawal symptoms from oral or intrathecal baclofen). Consult the technical manual of the implantable infusion system for additional post-implant clinician and patient information.”<sup>1</sup>

Figure 1

## Clinical Guidelines

Table 5 summarizes the current clinical practice guidelines available on the Agency of Healthcare and Research Quality website (AHRQ; guidelines.gov) and the National Institute for Health and Clinical Excellence (NICE) website about the use of intrathecal baclofen. There were only 2 relevant guidance documents identified on these websites regarding the use of intrathecal baclofen (for the treatment of spasticity in children and adolescents/young people with cerebral palsy/non-progressive brain disorders). A third guideline was included for MS where baclofen is mentioned, but not intrathecal baclofen.

The 2013 National Institute for Health and Clinical Excellence (NICE) guideline for stroke rehabilitation does not mention intrathecal baclofen.<sup>29</sup> Physiotherapy is recommended for patients with movement difficulties.<sup>29</sup> Various strategies and considerations are discussed including strength training, fitness training, wrist and hand splints, electrical stimulation, constraint-induced movement therapy, shoulder pain, repetitive task training, walking therapies (treadmill with or without body weight support), electromechanical gait training, ankle-foot orthoses, and electrical stimulation (lower limb).<sup>29</sup> A NICE technology appraisal of botulinum toxin A for treating upper or lower limb spasticity associated with stroke is currently in progress.<sup>30</sup>

The 2010 Practice Parameter from the American Academy of Neurology and the Child Neurology Society on the pharmacologic treatment of spasticity in children and adolescents with cerebral palsy, states that there are insufficient data to support or refute use of oral baclofen, or continuous intrathecal baclofen.<sup>31</sup>

Not all patients would benefit from spasticity reduction and some may experience a decline in function. The authors of the practice parameter therefore state that this needs to be a decision based on a careful assessment of the patient’s other impairments such as movement disorders and weakness, the type of treatment and use thereof.<sup>31</sup> They also list reasons for treatment of spasticity:

- To reduce pain and muscle spasms
- To facilitate brace use
- To improve posture

- To minimize contractures and deformity
- To facilitate mobility and dexterity
- To improve patient ease of care and hygiene/self-care<sup>31</sup>

The 2012 NICE guidance is also intended for use in children. It focuses on children that have spasticity because of a “non-progressive brain disorder, including those with spasticity resulting from cerebral palsy and those with spasticity resulting from a non-progressive brain injury acquired later in childhood or adolescence.” Authors state that intrathecal baclofen is not intended for patients with progressive brain disorders, but that many of the recommendations might also apply. In addition, it is not intended for use in adults, or children with pure dystonia or other motor disorders which do not co-exist with spasticity.<sup>32</sup>

The principles of care in NICE guidance for spasticity in children and young people with non-progressive brain disorders, include access to a network of care. This includes professionals with experience in the care of patients with spasticity and local expertise in pediatrics, nursing, physiotherapy and occupational therapy. It also includes access locally or regionally to orthototics, orthopedic surgery, and/or neurosurgery and pediatric neurology.<sup>32</sup>

Recommendations include that management be individualized, goal focused, and developed and implemented in partnership with the child or young person and their parents’ consideration of the impact on the patient and their family. Recommendations exist for support services such as timely access to the necessary equipment, and monitoring which includes response to treatments, worsening of spasticity, developing secondary consequences of spasticity (e.g., pain or contractures), those at increased risk of hip displacement and the need to change their individualized goals.<sup>32</sup>

NICE guidance include intrathecal baclofen as a treatment option if patients are still experiencing difficulties despite the use of non-invasive treatments, but state that typically, patients that would benefit from continuous pump-administered intrathecal baclofen have moderate or severe motor function problems (GMFCS level III, IV, or V) and bilateral spasticity affecting upper and lower limbs.<sup>32</sup> Gross Motor Function Classification System or GMFCS describes the gross motor function of patients with cerebral palsy, and considered the “standard for mobility assessment and ambulatory ability prediction” in these patients.<sup>33</sup> It is recommended to balance the benefits of reducing spasticity with the risk of lost function (spasticity sometimes supports function by compensating for muscle weakness).<sup>32</sup>

Note that the NICE Guideline Development Group made a research recommendation to investigate the clinical and cost effectiveness of continuous pump-administered intrathecal baclofen compared to usual care in children and young people (under 19s) who are at GMFCS level IV or V, to improve future guidance and care. They suggest randomised controlled trials, prospective cohort studies and qualitative studies that have the following outcomes: “quality of life; reduction of pain; reduction of tone; acceptability and tolerability; participation or inclusion; and adverse effects and their association with any potential predisposing factors.”<sup>34</sup>

**Table 2. Clinical guidance for the use of intrathecal baclofen**

Guideline	Recommendations
<p><b>2010 Practice parameter from the American Academy of Neurology (AAN) and the Child Neurology Society.<sup>31</sup></b>  Pharmacologic treatment of <u>spasticity in children and adolescents with cerebral palsy</u> (an evidence-based review; literature search 1966 to July 2008)  <b>Current guideline. Reaffirmed on July 13, 2013.<sup>35</sup></b></p>	<p>“For localized/segmental spasticity that warrants treatment, botulinum toxin type A should be offered as an effective and generally safe treatment (Level A).”</p> <p>There are insufficient data to support or refute the use of phenol, alcohol, or botulinum toxin type B (Level U).</p> <p>For generalized spasticity that warrants treatment, diazepam should be considered for short-term treatment, with caution regarding toxicity (Level B), and tizanidine may be considered (Level C). <u>There are insufficient data to support or refute use of dantrolene, oral baclofen, or continuous intrathecal baclofen (Level U).”</u></p>
<p><b>National Institute for Health and Clinical Excellence (NICE) guideline; no. 145 (NGC:009484 2012 Jul)<sup>32</sup></b>  <u>Spasticity in children and young people (under 19s) with non-progressive brain disorders: management of spasticity and co-existing motor disorders and their early musculoskeletal complications.</u></p> <p>Note: Developed by the National Collaborating Centre for Women's and Children's Health (NCC-WCH) on behalf of the National Institute for Health and Clinical Excellence (NICE).</p>	<p>Please refer to guidelines for complete recommendations.</p> <p>Specific adapted physical therapy programs are recommended as essential following treatment with continuous pump-administered intrathecal baclofen (and botulinum toxin A, orthopedic surgery, or selective dorsal rhizotomy).</p> <p><u>“Consider treatment with continuous pump-administered intrathecal baclofen in children and young people with spasticity if, despite the use of non-invasive treatments, spasticity or dystonia are causing difficulties with any of the following:</u></p> <ul style="list-style-type: none"> <li>• Pain or muscle spasms</li> <li>• Posture or function</li> <li>• Self-care (or ease of care by parents or carers)”</li> </ul> <p>An intrathecal test dose administered using a catheter inserted under general anaesthesia in a specialist neurosurgical center with expertise to carry out the necessary assessments and in an inpatient setting (to support reliable assessment of safety and effectiveness) is recommended. Spasticity, dystonia, presence of pain or muscle spasms, postural difficulties, functional difficulties, and self-care should be assessed before the test as relevant to the treatment goals, and reduction or improvements in these should be assessed 3-5 hours after administration (or when not sedated anymore) by the same healthcare professionals to decide whether the response is satisfactory.</p> <p>Following a satisfactory response to the test, it is recommended to implant the infusion pump and start treatment with continuous pump-administered intrathecal baclofen within 3 months. Monitoring continuous pump-administered baclofen response as relevant to treatment goals preferably by the same healthcare professionals is recommended, and to titrate the dose if necessary to optimize effectiveness. In the case of unsatisfactory responses, placement of the catheter and potential technical faults should be checked for, and if no problems are identified, the dose should be gradually reduced (and monitored for changes in spasticity and associated symptoms). Alternative management options should be considered if the continuous pump-administered intrathecal baclofen therapy is unsatisfactory.</p>

Guideline	Recommendations
<p><b>National Institute for Health and Clinical Excellence (NICE) guideline; [CG186] NGC:010569 2004 (revised 2014 Oct)<sup>36</sup></b></p> <p><u>Multiple sclerosis: management of multiple sclerosis in primary and secondary care.</u></p> <p>Note: Developed by the National Clinical Guideline Centre (NCGC) on behalf of the National Institute for Health and Care Excellence (NICE).</p>	<ul style="list-style-type: none"> <li>• Contraindications, comorbidities, patient preferences and tolerability of drugs should be considered</li> <li>• Baclofen or gabapentin is recommended first-line to treat spasticity in MS with no reference to intrathecal baclofen</li> </ul>

*"Classification of Recommendations: A = Established as effective, ineffective or harmful (or established as useful/predictive or not useful/predictive) for the given condition in the specified population. (Level A rating requires at least two consistent Class I studies.)\*\* B = Probably effective, ineffective or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population. (Level B rating requires at least one Class I study or two consistent Class II studies.) C = Possibly effective, ineffective or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population. (Level C rating requires at least one Class II study or two consistent Class III studies.) U = Data inadequate or conflicting; given current knowledge, treatment (test, predictor) is unproven. \*\*In exceptional cases, one convincing Class I study may suffice for an "A" recommendation if 1) all criteria are met, 2) the magnitude of effect is large (relative rate improved outcome >5 and the lower limit of the confidence interval is >2)."*<sup>37</sup>

*"AAN Classification of Evidence for Therapeutic Intervention: Class I: Randomized, controlled clinical trial with masked or objective outcome assessment, in a representative population. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences. The following are required: (a) concealed allocation; (b) primary outcome(s) clearly defined; (c) exclusion/inclusion criteria clearly defined; and (d) adequate accounting for drop-outs (with at least 80% of enrolled subjects completing the study) and cross-overs with numbers sufficiently low to have minimal potential for bias. Class II: Prospective matched group cohort study in a representative population with masked outcome assessment that meets b-d above OR a RCT in a representative population that lacks one criteria a-d. Class III: All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome is independently assessed, or independently derived by objective outcome measurement. \*\* Class IV: Studies not meeting Class I, II, or III criteria, including consensus, expert opinion, or a case report."*<sup>38</sup>

### Other recommendations - Poststroke

A 2006 consensus statement on the use of intrathecal baclofen therapy in poststroke spastic hypertonia was identified in PubMed.<sup>39</sup> Please also refer to the Cochrane systematic review information included in the next section (Lindsay et al.<sup>40</sup>; also table 3 in appendix 1).

Publication	Expert information and financial support	Recommendations
<p><b>Francisco GE, et al. Consensus Panel Guidelines for the Use of Intrathecal Baclofen Therapy in Poststroke Spastic Hypertonia (2006)<sup>39</sup></b></p>	<p>Note that these statements and recommendations were made by 6 experts (three physiatrists, two neurologists, and one physical therapist) who are/were managing ITB therapy in at least 175 stroke survivors. These experts were also involved in research and publications on ITB. They convened in Minneapolis, Minnesota, on April 30 and May 1, 2005 and the meeting was financially supported by Medtronic, Inc.</p>	<ul style="list-style-type: none"> <li>• Evidence is limited by small sample sizes and study design</li> <li>• Based on these studies ITB has a role in decreasing impairment (spastic hypertonia) and improving function</li> <li>• Authors state that "These preliminary findings corroborate the positive clinical experience with ITB therapy."</li> <li>• "Preferred candidates for ITB therapy include stroke survivors whose spastic hypertonia did not respond adequately to other treatment interventions or who did not tolerate the adverse effects of other therapies and who are motivated to participate in long-term ITB management."</li> </ul>

## Systematic review evidence

Tables 1 to 3 in Appendix 1 contain information from relevant systematic reviews identified in the Cochrane Library. Tables 1 and 2 contain information on systematic reviews that focused on intrathecal baclofen and table 3 contains information on pharmacological interventions/treatments for spasticity.

Authors of a recent (2015) Cochrane review on the effectiveness of intrathecal baclofen for treating spasticity in children with cerebral palsy, found some limited evidence that it is effective in the short-term.<sup>2</sup> The authors state small studies and methodological issues in some studies limit the validity of the evidence, and that consideration should be given to the broader context when considering effectiveness. More evidence is needed not only for improvements in spasticity, but also for ease of care, and to determine whether it increases gross motor function, or improves comfort, ease of care, and quality of life. There is some evidence (limited by small sample size and methodological issues) that it may be effective when these outcomes are considered as the aims of therapy. The included studies were of short duration so intrathecal baclofen's long-term safety could not be determined (one 6-month study using an implantable pump and 4 shorter term studies administered via short-term means i.e., lumbar puncture). The authors could also not reach a conclusion on whether the subsequent need for orthopedic surgery is altered in children receiving baclofen therapy because the studies were short-term RCTs.<sup>2</sup>

McIntyre et al. (2014 systematic review that met the inclusion criteria for the Database of Abstracts of Reviews of Effects; DARE) reviewed the effectiveness of intrathecal baclofen in the treatment of spasticity in individuals with spinal cord injuries (SCIs) at least 6 months post-injury or diagnosis.<sup>41</sup> They included 8 non-RCTs that included 162 patients. The authors found evidence that intrathecal baclofen is effective in these patients, but the studies were of lower methodological quality and they suggest that additional high quality evidence is needed. Complications, adverse effects, and malfunction of the device are discussed. The authors suggest considering available treatment options and conclude that even though intrathecal baclofen may be safe and effective for most patients, it should be reserved for those who are refractory to conservative treatments and physical therapy.<sup>41</sup>

Lindsay et al. in a recent Cochrane review (2016) regarding pharmacological interventions (other than botulinum toxin) for spasticity after stroke, found insufficient evidence to make any conclusions and warn about the potential for adverse effects of antispasmodics. None of the studies meeting inclusion criteria evaluated intrathecal baclofen. The authors mention a 2010 systematic review by Olvey et al.<sup>42</sup> that included 54 studies; mainly involving botulinum toxin (51 studies) and the others were uncontrolled trials of tizanidine and intrathecal baclofen, and one cross-over trial investigating intrathecal baclofen. These intrathecal baclofen studies were excluded from Cochrane review (did not meet inclusion criteria).

Insufficient evidence exists for interventions to manage spasticity following traumatic brain injury (Cochrane review: Synnot A, et al. 2017)<sup>11</sup> and in patients with amyotrophic lateral sclerosis/motor neuron disease (Summary of Cochrane reviews: Ng L, et al. 2017).<sup>43</sup>

## Factors to consider

- **Not first-line therapy for spasticity:** It should be reserved for patients unresponsive to oral baclofen or for those who cannot tolerate therapeutic oral doses due to intolerable CNS side effects at effective doses.<sup>6,28</sup>
- **Spasticity due to traumatic brain injury:** It is recommended in the product label to wait at least one year after the injury before consideration of long term intrathecal baclofen therapy.<sup>6</sup>
- **Uses other than spasticity:** Off-label (investigational)
- **Route of administration of ITB:** ONLY intrathecal<sup>1,6</sup>
- **Phases that must occur in a medically supervised and adequately equipped environment (including resuscitation equipment):** Screening procedure (test dose) and adjustment of dosage following pump implantation<sup>1</sup>
- **Test dose:** Patients have to receive a test dose (intrathecal single bolus test doses via spinal catheter or lumbar puncture) and must show a response in a screening trial before a device is implanted for continuous use.<sup>6</sup> Those who do not respond to a 100mcg test dose, should not receive continuous treatment.
- **Chronic use (in implantable pumps):** Only Medtronic SynchroMed II Programmable pump or other pumps approved by the FDA specifically for the administration of Lioresal® or Gablofen Intrathecal into the intrathecal space should be used.<sup>1,6</sup> The product label states that physicians must be adequately trained and educated in chronic intrathecal infusion therapy (there is a potential for life-threatening CNS depression, cardiovascular collapse, and/or respiratory failure).<sup>1</sup>
- **Refilling the pump:** Extreme caution is advised when refilling the pump i.e. to only refill the Medtronic SynchroMed II Programmable Pump through the reservoir refill septum and NOT through the catheter access port (direct access to intrathecal catheter) as this may cause life-threatening overdose.<sup>1</sup> The instruction manual for the Medtronic refill kit (included with the Lioresal label) include details about the refill procedures, warnings and precautions, and emergency procedures.<sup>6</sup> The appropriate manufacturer's manual should be referred to for specific instructions and precautions for refilling the reservoir and programming the pump.<sup>1</sup>
- **Prescriber, Caregiver, and Patient Training:** The product label states: "It is mandatory that the patient, all patient caregivers, and the physicians responsible for the patient receive adequate information regarding the risks of mode of treatment. All medical personnel and caregivers should be instructed in 1) the signs and symptoms of overdose, 2) procedures to be followed in the event of overdose and 3) proper home care of the pump and insertion site."<sup>1</sup> Patients with signs of overdose should be taken to the hospital for assessment.<sup>1</sup>
- **Clinic visits:** NICE guidance include that patients and their carers be informed about the implant procedure, the need for regular hospital follow-up visits, the requirements for pump maintenance, and the risks/complications associated with intrathecal baclofen.<sup>32</sup> Refills and medication adjustments require visits every few months which could be every 1 to 6 months.<sup>6</sup> The Medtronic refill kit instructions for use in the Lioresal product label states that the patient must return to the clinic for refills at the prescribed times.<sup>6</sup> Initially the period could be longer because of dose titration. The system will be removed and replaced at the end of the battery's life span (usually 5 to 7 years).<sup>44</sup> NICE guidance suggest to gradually reduce the dose as the infusion pump approaches the end of its expected lifespan to enable the patient or their parents or carers to decide whether or not to have a new pump implanted.<sup>32</sup>
- **Special populations:** Elderly patients may be more sensitive to adverse CNS effects. Both products are indicated for use in children older than 4 years old because the safety has not been

established for use in younger children. Implanting the pump in children require sufficient body mass to accommodate the pump.<sup>1,6</sup>

Pregnancy Category C (no adequate or well-controlled studies in pregnant women, but may cause fetal harm based on animal studies); baclofen is excreted in human milk; effect on labor and delivery unknown.<sup>1</sup>

- **Compounding intrathecal baclofen from baclofen powder:** Baclofen powder could be used to compound oral, topical or intrathecal dosage forms. It is outside legitimate practice to compound medication that is commercially available.<sup>45</sup> It may be appropriate/medically necessary to compound intrathecal baclofen if it is not available commercially, which may be the case if the requested strength is not commercially available or not available commercially due to shortage (some plans have prior authorization criteria for baclofen powder to ensure appropriate use including a limit on the maximum concentration allowed based on FDA approved product labeling).<sup>45,46</sup> Concerns exist about risks associated with compounded intrathecal baclofen such as contamination (given the risk of meningitis) and erroneous concentrations. Moberg-Wolff in a random sample of 29 compounded intrathecal baclofen preparations from 6 pharmacies in the United States found a high incidence of concentration inaccuracies with 22% of samples more than 10% above or below labeled concentration, and over 40% were more than 5% above or below labeled concentration versus no concentration deviations and consistent drug density for the commercial products tested.<sup>45</sup> The author also states that they did not test sample sterility in their study, but that none of the pharmacies did before shipping, and that was concerning.<sup>45</sup> Expiration dates of compounded products varied (14-90 days) and some indicated stability for 90 days in the pump, but this was not supported by any other data apart from references to commercial product labeling. The author states that the Lioresal Intrathecal's expiration date once in the 40-mL delivery device was 6 months (or 3 years from manufacture).<sup>45</sup> It should be noted that these pharmacies were known suppliers of many office or hospital practices and had references from physicians and hospitals using their products. Risks should be explained to patients and informed consent obtained if compounded products are used.<sup>45</sup>

## Utah Medicaid Utilization Data

The utilization data for intrathecal baclofen for the last 3 years (2015-01-01 to 2017-12-31) is presented as follows:

- A. Total utilization data (All patients)  
Table 3 showing total utilization by prescription claims and CPT codes and the combined total
- B. Pediatric utilization data  
Table 4 showing total utilization by prescription claims and CPT codes and the combined total
- C. Pharmacy claims  
Table 5 showing pharmacy claims for intrathecal baclofen  
Prescriber details
- D. AGE AND SEX of patients for whom there were claims for intrathecal baclofen
- E. The number of patients that received intrathecal baclofen that had select diagnosis codes submitted
  - The select diagnosis codes used were for severe spasticity and were based on those that Medtronic provides as information on commonly billed codes for FDA-approved indications. They provide this information for convenience, but state that it is not legal advice or a recommendation, but rather to assist and to contact payers for specific policies. The document states that "ITB Therapy is directed at reducing the symptom of severe spasticity. Because symptom codes are generally not acceptable as the principal diagnosis, the principal diagnosis is coded to the underlying condition as shown." Please refer to page 4 and 5 of the original document <http://www.medtronic.com/content/dam/medtronic-com/professional/documents/tdd-reimbursement-coding-2017-uc201002982men.pdf> for the comprehensive list of all diagnosis codes captured.
- F. Compounded intrathecal baclofen

## Summary

### All patient summary

- 176 unique patients received intrathecal baclofen during this timeframe, and there were 1032 claims. Some patients have fills across multiple years, but not all of them.
- 13 patients have a CPT code submitted for the test dose (J0476) during this timeframe (some may have received the test dose prior to this time frame if they entered into 2015 already on ITB)
- 146/176 patients that received intrathecal baclofen are under 45 years old, and there are a few patients >64 years old (<5) that may be more at risk for adverse CNS effects
- Most prescription claims were for Gablofen (20000/20 and 40000/20)



**Pediatric patient summary**

- 37 pediatric patients (<18 years old; 20 male and 17 female) received intrathecal baclofen during this timeframe, and there were 164 claims
- <5 patients are younger than 4 years old (safety has not been established in this population)
- Similar to all patients, most prescription claims were for gablofen (20000/20 and 40000/20)

**Pharmacy claims summary**

- There were around 110 pharmacy claims for 14 patients filled at 5 pharmacies
- The 5 pharmacies appear to serve hospitals, nursing facilities, assisted livings/home care programs, and hospices.
- 8/14 were pediatric patients
- None of these patients were >64 years old

**Diagnosis codes submitted**

- Please refer to section E

### A. Table 3. All patients

#### Intrathecal baclofen - RX CLAIMS

AGENT	PRODUCT	2015		2016		2017*		ALL	
		CLAIMS	PATIENTS	CLAIMS	PATIENTS	CLAIMS	PATIENTS	CLAIMS	PATIENTS
Baclofen	GABLOFEN INJ 10000/20	6	<5	29	9	22	6	57	<16
Baclofen	GABLOFEN INJ 20000/20	59	26	35	15	25	15	119	43
Baclofen	GABLOFEN INJ 40000/20	214	64	230	59	204	57	648	98
Baclofen	GABLOFEN INJ 50MCG/ML	8	<5	<5	<5	5	<5	17	9
Baclofen	LIORESAL INT INJ 10MG/20	–	–	<5	<5	<5	<5	<5	<5
Baclofen	LIORESAL INT INJ 40MG/20	4	<5	<5	<5	<5	<5	8	6
Total Rx		291	90	300	82	261	76	<854	138

#### Intrathecal baclofen - CPT CLAIMS

J0475	INJECTION, BACLOFEN, 10 MG	120	63	29	20	31	23	180	78
J0475 with Rx	INJECTION, BACLOFEN, 10 MG	185	83	192	79	189	73	566	130
Total CPT		305	125	221	89	220	88	746	170
Total Rx + CPT		411	128	329	92	292	91	1,032	176

### B. Table 4. Pediatric patients

## Intrathecal baclofen - RX CLAIMS

AGENT			2015		2016		2017*		ALL	
PRODUCT			CLAIMS	PATIENTS	CLAIMS	PATIENTS	CLAIMS	PATIENTS	CLAIMS	PATIENTS
Baclofen	GABLOFEN	INJ 10000/20	-	-	<5	<5	<5	<5	<5	<5
Baclofen	GABLOFEN	INJ 20000/20	15	8	<5	<5	7	5	26	13
Baclofen	GABLOFEN	INJ 40000/20	45	12	37	11	44	15	126	25
Baclofen	GABLOFEN	INJ 50MCG/ML	-	-	<5	<5	5	<5	6	<5
Baclofen	LIORESAL INT	INJ 40MG/20	<5	<5	-	-	-	-	<5	<5
Total Rx			<65	<23	43	16	<61	20	161	36

## Intrathecal baclofen - CPT CLAIMS

J0475 without Rx	INJECTION, BACLOFEN, 10 MG	<5	<5	–	–	–	–	<5	<5
J0475 with Rx	INJECTION, BACLOFEN, 10 MG	39	19	31	14	49	17	119	31
Total CPT		<44	<22	31	14	49	17	<124	<34

<b>Total (Rx + CPT)</b>	<b>64</b>	<b>20</b>	<b>43</b>	<b>16</b>	<b>57</b>	<b>20</b>	<b>164</b>	<b>37</b>
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## C. Table 5. Pharmacy claims

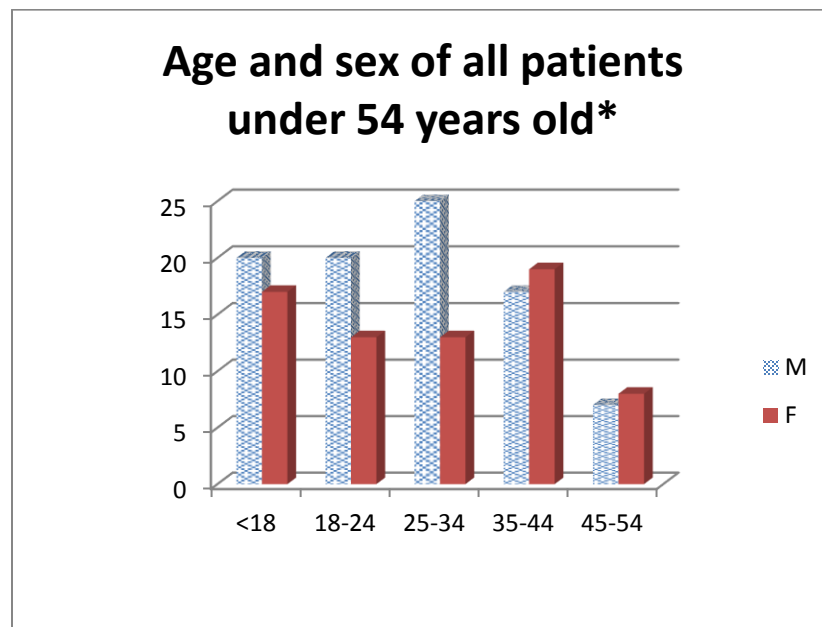
### Intrathecal baclofen - PHARMACY CLAIMS

AGENT	PRODUCT	CLAIMS	2015		2016		2017*		ALL	
			PATIENTS	CLAIMS	PATIENTS	CLAIMS	PATIENTS	CLAIMS	PATIENTS	CLAIMS
Baclofen	GABLOFEN INJ 10000/20	17	5	<5	<5	5	<5	25	7	
Baclofen	GABLOFEN INJ 20000/20	—	—	—	—	<5	<5	<5	<5	
Baclofen	GABLOFEN INJ 40000/20	30	6	29	6	20	5	79	7	
<b>Total</b>		<b>47</b>	<b>11</b>	<b>&lt;34</b>	<b>&lt;11</b>	<b>&lt;30</b>	<b>8</b>	<b>&lt;109</b>	<b>14</b>	

PRESCRIBER SPECIALTY TYPE	TOTAL CLAIMS 2014-17
Physical Medicine	~30%
Pediatrics	~70%

## D. Age and gender - All patients

AGE*	M	F	Total
<18	20	17	37
18-24	20	13	33
25-34	27	13	40
35-44	17	19	36
45-54	7	8	15
55-64	<5	7	<12
>64	<5	<5	<5
TOTAL	<98	<82	



\*Fewer than 5 patients were male, female, or both in the over 54 years old patients so are not shown in the chart.

## E. Patients with diagnosis codes submitted for severe spasticity

AGE GROUP	Cerebral Palsy <sup>a</sup>	Multiple Sclerosis (MS) <sup>b</sup>	Other Severe Spasticity <sup>c</sup>	Sequela (Late Effect) of Prior Injury <sup>d</sup>	Sequela (Late Effect) of Cerebrovascular Accident <sup>e</sup>	Total number of patients with one of these dx codes submitted	Total number of patients that received intrathecal baclofen
<18	31	0	13	<5	0	<b>32</b>	<b>37</b>
18-24	27	0	13	<5	0	<b>31</b>	<b>33</b>
25-34	24	<5	30	9	0	<b>38</b>	<b>40</b>
35-44	19	<5	23	9	<5	<b>32</b>	<b>36</b>
45-54	<5	<5	11	<5	<5	<b>12</b>	<b>15</b>
55-64	<5	<5	8	<5	<5	<b>11</b>	<b>&lt;12</b>
>64	0	<5	<5	<5	<5	<b>&lt;5</b>	<b>&lt;5</b>
<b>Total</b>	<b>105</b>	<b>11</b>	<b>&lt;103</b>	<b>28</b>	<b>8</b>	<b>&lt;161</b>	<b>176</b>

\* Age at first claim.

<sup>a</sup> Severe Spasticity of Cerebral Origin: Cerebral palsy

<sup>b</sup> Severe Spasticity of Spinal Origin: Multiple Sclerosis

<sup>c</sup> Other Severe Spasticity of Spinal or Cerebral Origin (hemiplegia, paraplegia, quadriplegia, diplegia, monoplegia, paralytic syndrome)

<sup>d</sup> Intracranial/traumatic brain injury, spinal cord injury

<sup>e</sup> Severe Spasticity of Cerebral Origin: Sequela (Late Effect) of Cerebrovascular Accident (following hemorrhagic or ischemic stroke; hemiplegia and hemiparesis, monoplegia, other paralytic syndrome/quadruplegia, ataxia)

- <161/176 patients had one of these diagnosis codes submitted
- Most pediatric patients and those in the 18-24 year old category had a diagnosis code submitted for cerebral palsy
- The 25-44 year old adult patients had mostly codes submitted for cerebral palsy or other severe spasticity, with only some for injuries, and a few for cerebrovascular accidents and MS

## F. Compounded intrathecal baclofen

All the prescription claims found for intrathecal baclofen were for brand names (Gablofen or Lioresal) and none were identified for compounded intrathecal baclofen. The CPT codes are for intrathecal baclofen with no specific brand names so it is unknown whether compounded products were used.

Entries for Gablofen powder was found in the Medicaid NDC drug list with “not applicable” entered in the route of administration field. There are 8 distinct patients that had 23 claims for baclofen in powdered form. The fields in the claims table were reviewed, but no additional information was found to determine whether these claims could be for compounded intrathecal baclofen or other routes of use (e.g. topical, oral). This is a potential area for future investigation—the off-label use of baclofen in compounded topical formulations which is seen in pain management.

We explored whether any claims were submitted for Healthcare Common Procedure Coding System Code (HCPCSC) J7799 Not otherwise classified (Noc) drugs, other than inhalation drugs, administered through durable medical equipment (DME) or HCPCS code Q9977 (compound drug, NOC; effective with dates of service July 1, 2015 and after).<sup>47</sup> There are 89 patients that have a procedure code submitted for J7799 or Q9977. The fields in the claims table were reviewed, but no additional information was found to determine whether these claims could be for compounded intrathecal baclofen.

None of the patients with a powdered baclofen claim had a corresponding J7799 or Q9977 procedure code submitted.

## Conclusions

According to the 2010 Practice parameter from the American Academy of Neurology (AAN) and the Child Neurology Society, evidence was considered insufficient to support or refute the use of ITB for spasticity in children with CP.<sup>4,31</sup> NICE guidance include intrathecal baclofen as a treatment option if patients are still experiencing difficulties despite the use of non-invasive treatments, but state that typically, patients that would benefit from continuous pump-administered intrathecal baclofen have moderate or severe motor function problems (GMFCS level III, IV, or V) and bilateral spasticity affecting upper and lower limbs.<sup>32</sup>

ITB complications include infections, catheter problems, overdose, and baclofen withdrawal.<sup>8</sup> ITB should be reserved for patients unresponsive to oral baclofen or for those who cannot tolerate therapeutic oral doses due to intolerable CNS side effects at effective doses.<sup>6,28</sup> Appropriate use of compounded intrathecal powder needs to be ensured. Commercial intrathecal baclofen products should be used if available. All parties involved should have an adequate understanding of the risks of intrathecal baclofen treatment including how to recognize overdose and procedures to be followed, as well as proper home care of the pump and insertion site.<sup>1</sup>

## Appendix 1 – Systematic Reviews

**Table 1. Cochrane Systematic Review(s) – Focusing on intrathecal baclofen**

Authors	Title	Objectives	Main results	Conclusions
Hasnat MJ, Rice JE (2015) <sup>2</sup>	<u>Intrathecal baclofen for treating spasticity in children with cerebral palsy</u>	“To determine whether intrathecal baclofen is an effective treatment for spasticity in children with cerebral palsy.”	<p>“Six studies met the inclusion criteria. The data obtained were unsuitable for the conduct of a meta-analysis; we have completed a qualitative summary.</p> <p>All studies were found to have high or unclear risk of bias in some aspects of their methodology. Five of the six studies reported data collected in the randomised controlled phase of the study. A sixth study did not report sufficient results to determine the effect of intrathecal baclofen versus placebo. Of these five studies, four were conducted using lumbar puncture or other short-term means of delivering intrathecal baclofen. One study assessed the effectiveness of implantable intrathecal baclofen pumps over six months. The four short-term studies demonstrated that intrathecal baclofen therapy reduces spasticity in children with cerebral palsy. However, two of these studies utilised inappropriate techniques for statistical analysis of results. The single longer-term study demonstrated minimal reduction in spasticity with the use of intrathecal baclofen therapy.</p> <p>One of the short-term studies and the longer term study showed improvement in comfort and ease of care. The longer term study found a small improvement in gross motor function and also in some domains of health-related quality of life. Some caution is required in interpreting the findings of the all the studies in the review due to methodological issues. In particular, there was a high risk of bias in the methodology of the longer term study due to the lack of placebo use in the control group and the absence of blinding to the intervention after randomisation for both participants and investigators.”</p>	<p>“There is some limited short-term evidence that intrathecal baclofen is an effective therapy for reducing spasticity in children with cerebral palsy. The effect of intrathecal baclofen on long-term spasticity outcomes is less certain. The validity of the evidence for the effectiveness of intrathecal baclofen in treating spasticity in children with cerebral palsy from the studies in the review is constrained by the small sample sizes of the studies and methodological issues in some studies.</p> <p>Spasticity is a impairment in the domain of body structure and function. Consideration must also be given to the broader context in determining whether intrathecal baclofen therapy is effective. The aim of therapy may be, for example, to improve gross motor function, to increase participation at a social role level, to improve comfort, to improve the ease of care by others or to improve the overall quality of life of the individual. Intrathecal baclofen may improve gross motor function in children with cerebral palsy, but more reliable evidence is needed to determine this. There is some evidence that intrathecal baclofen improves ease of care and the comfort and quality of life of the individuals receiving it, but again small sample sizes and methodological issues in the studies mean that these results should be interpreted with caution.</p> <p>Further evidence of the effectiveness of intrathecal baclofen for treating spasticity, increasing gross motor function and improving comfort, ease of care and quality of life is needed from other investigators in order to validate these results. The short duration of the controlled studies included in this review did not allow for the exploration of questions regarding whether the subsequent need for orthopaedic surgery in children receiving intrathecal baclofen therapy is altered, or the safety and the economic implications of intrathecal baclofen treatment when long-term therapy is administered via an implanted device. Controlled studies are not the most appropriate study design to address these questions, cohort studies may be more appropriate.”</p>



**Table 2. Other Reviews included in the Cochrane Library: Centre for Reviews and Dissemination (CRD): Systematic reviews that meet the criteria for inclusion on *Database of Abstracts of Reviews of Effects (DARE)* – focusing on intrathecal baclofen**

Authors	Title	Objectives	Methods	Conclusions
McIntyre A, et al. (2014) <sup>41,48</sup>	Examining the effectiveness of <u>intrathecal baclofen</u> on spasticity in individuals with <u>chronic spinal cord injury</u> : a systematic review (Provisional abstract)	“To review the available evidence on the effectiveness of intrathecal baclofen in the treatment of spasticity in individuals with spinal cord injuries (SCIs) at least 6 months post-injury or diagnosis.”	Literature search: Pub Med, CINAHL, EMBASE limited to English “Studies were included for review if: (1) more than 50% of the sample size had suffered a traumatic or non-traumatic SCI; (2) there were more than three subjects; (3) subjects received continuous intrathecal baclofen via an implantable pump aimed at improving spasticity; and (4) all subjects were ≥6 months post-SCI, at the time of the intervention.” “Methodological quality was assessed using the PEDro for randomized-controlled trials (RCTs) and the Downs and Black (D&B) tool for non-RCTs. A level of evidence was assigned to each intervention using a modified Sackett scale.”	“The literature search resulted in 677 articles. No RCTs and eight non-RCTs (D&B scores 13-24) met criteria for inclusion, providing a pooled sample size of 162 individuals. There was substantial level 4 evidence that intrathecal baclofen is effective in reducing spasticity. Mean Ashworth scores reduced from 3.1-4.5 at baseline to 1.0-2.0 (P < 0.005) at follow-up (range 2-41 months). Average dosing increased from 57-187 µg/day at baseline to 218.7-535.9 µg/day at follow-up. Several complications from the use of intrathecal baclofen or pump and catheter malfunction were reported.”

**Table 3. Cochrane Systematic Review(s) – Interventions/symptomatic treatments for spasticity**

Authors	Title	Objectives	Main results	Conclusions
Lindsay C, et al. (2016) <sup>40</sup>	Pharmacological interventions other than botulinum toxin for spasticity after stroke	“To assess if <u>pharmacological interventions for spasticity</u> are more effective than no intervention, normal practice, or control at improving function <u>following stroke.</u> ”	“We included seven RCTs with a total 403 participants. We found a high risk of bias in all but one RCT. Two of the seven RCTs assessed a systemic drug versus placebo. We pooled data on an indirect measure of spasticity (160 participants) from these two studies but found no significant effect (odds ratio (OR) 1.66, 95% confidence interval (CI) 0.21 to 13.07; I <sup>2</sup> = 85%). We identified a significant risk of adverse events per participant occurring in the treatment group versus placebo group (risk ratio (RR) 1.65, 95% CI 1.12 to 2.42; 160 participants; I <sup>2</sup> = 0%). Only one of these studies used a functional outcome measure, and we found no significant difference between groups.	“The lack of high-quality RCTs limited our ability to make specific conclusions. Evidence is insufficient to determine if systemic antispasmodics are effective at improving function following stroke.”  <b>Implications for practice:</b> “There is currently insufficient high-quality evidence to make generalisable conclusions about the effect of pharmacological interventions on spasticity in people with stroke. Furthermore, we found some very low-quality evidence that suggests there is an increased risk of adverse effects in people who take antispasmodics when compared with placebo. We therefore cannot recommend pharmacological interventions as first-line treatment for people with spasticity after stroke. If a clinical

Authors	Title	Objectives	Main results	Conclusions
			<p>Of the other five studies, two assessed a systemic drug versus another systemic drug, one assessed a systemic drug versus local drug, and the final two assessed a local drug versus another local drug.”</p> <p>The authors listed the potential treatment drugs and included intrathecal baclofen in their search strategy. Intrathecal baclofen was not evaluated in any of the included studies. The authors state: “Despite the variety of drugs that are currently used clinically to treat spasticity, only three different drugs (tolperisone, tizanidine, and phenol) were investigated against four different control drugs (diazepam, baclofen, botulinum toxin, and alcohol).”</p>	<p>decision is made to administer any of these interventions, particular care should be taken to monitor for adverse effects.”</p>
Synnot <i>a, et al.</i> (2017) <sup>11</sup>	<u>Interventions for managing skeletal muscle spasticity following traumatic brain injury</u>	“To assess the effects of interventions for managing skeletal muscle spasticity in people with TBI.”	<p>“We included nine studies in this review which involved 134 participants with TBI. Only five studies reported between-group differences, yielding outcome data for 105 participants with TBI. These five studies assessed the effects of a range of pharmacological (baclofen, botulinum toxin A) and non-pharmacological (casting, physiotherapy, splints, tilt table standing and electrical stimulation) interventions, often in combination. The studies which tested the effect of baclofen and tizanidine did not report their results adequately. Where outcome data were available, spasticity and adverse events were reported, in addition to some secondary outcome measures.</p> <p>Of the five studies with results, three were funded by governments, charities or health services and two were funded by a pharmaceutical or medical technology company. The four studies without useable results were funded by pharmaceutical or medical technology companies.</p> <p>It was difficult to draw conclusions about the effectiveness of these interventions due to poor reporting, small study size and the fact that participants with TBI were usually only a</p>	<p>“The very low quality and limited amount of evidence about the management of spasticity in people with TBI means that we are uncertain about the effectiveness or harms of these interventions. Well-designed and adequately powered studies using functional outcome measures to test the interventions used in clinical practice are needed.”</p>

Authors	Title	Objectives	Main results	Conclusions
			proportion of the overall total. Meta-analysis was not feasible due to the paucity of data and heterogeneity of interventions and comparator groups. Some studies concluded that the intervention they tested had beneficial effects on spasticity, and others found no difference between certain treatments. The most common adverse event was minor skin damage in people who received casting. We believe it would be misleading to provide any further description of study results given the quality of the evidence was very low for all outcomes."	
Ng L, et al. (2017) <sup>43</sup>	<u>Symptomatic treatments for amyotrophic lateral sclerosis/motor neuron disease</u>	"To summarise the evidence from Cochrane Systematic Reviews of all symptomatic treatments for MND."	<p>"We included nine Cochrane Systematic Reviews of interventions to treat symptoms in people with MND. Three were empty reviews with no included randomised controlled trials (RCTs); however, all three reported on non-RCT evidence and the remaining six included mostly one or two studies. We deemed all of the included reviews of high methodological quality."</p> <p>Please refer to the publication for additional information. Only the information relevant to spasticity has been included here:</p> <p><b>"Treatment for spasticity"</b></p> <p>It is uncertain whether an endurance-based exercise programme improved spasticity or quality of life, measured at three months after the programme, as the quality of evidence is very low (1 RCT, comparison "usual activities", N = 25). The review did not evaluate other approaches, such as use of baclofen as no RCTs were available."</p>	<p>"This overview has highlighted the lack of robust evidence in Cochrane Systematic Reviews on interventions to manage symptoms resulting from MND. It is important to recognise that clinical trials may fail to demonstrate efficacy of an intervention for reasons other than a true lack of efficacy, for example because of insufficient statistical power, the wrong choice of dose, insensitive outcome measures or inappropriate participant eligibility. The trials were mostly too small to reliably assess adverse effects of the treatments. The nature of MND makes it difficult to research clinically accepted or recommended practice, regardless of the level of evidence supporting the practice. It would not be ethical, for example, to design a placebo-controlled trial for treatment of pain in MND or to withhold multidisciplinary care where such care is available. It is therefore highly unlikely that there will ever be classically designed placebo-controlled RCTs in these areas. We need more research with appropriate study designs, robust methodology, and of sufficient duration to address the changing needs—of people with MND and their caregivers—associated with MND disease progression and mortality. There is a significant gap in studies assessing the effectiveness of interventions for symptoms relating to MND, such as pseudobulbar emotional lability and cognitive and behavioural difficulties. Future studies should use appropriate outcome measures that are reliable, have internal and external validity, and are sensitive to change in what is being measured (such as quality of life)."</p>

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